

L9 ANSWER 3 OF 24 MEDLINE
AN 1999221891 MEDLINE
DN 99221891
TI Blocking HIV-1 infection with **intrakines** [news].
AU Dorrell S
SO MOLECULAR MEDICINE TODAY, (1999 Mar) 5 (3) 97.
Journal code: CMK. ISSN: 1357-4310.
CY ENGLAND: United Kingdom
DT News Announcement
LA English
FS Priority Journals
EM 199910
EW 19991004

L9 ANSWER 9 OF 24 MEDLINE DUPLICATE 1
AN 1998430728 MEDLINE
DN 98430728
TI Anti-HIV type 1 activity of wild-type and functional defective RANTES **intrakine** in primary human lymphocytes.
AU Yang A G; Zhang X; Torti F; Chen S Y
CS Department of Cancer Biology, Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.
NC 1R01-AI41959-01 (NIAID)
SO HUMAN GENE THERAPY, (1998 Sep 20) 9 (14) 2005-18.
Journal code: A12. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB We have developed a genetic "**intrakine**" strategy to inactivate the CC-chemokine receptor 5 (CCR-5), the principal coreceptor for macrophage (M)-tropic HIV-1 viruses (Yang et al, 1997). The inactivation of CCR5 was achieved by targeting a modified CC-chemokine (RANTES) to the lumen of the endoplasmic reticulum (ER) to block the transport of the newly synthesized CCR-5. The transduced lymphocytes with the phenotypic CCR5 knockout were shown to be resistant to M-tropic HIV-1 infection.
This study illustrated the feasibility of the **intrakine** strategy to block HIV-1 infection. In our current study, the potential clinical application of the **intrakine** approach was further evaluated in human peripheral blood lymphocytes (PBLs). PBLs were transduced with the RANTES **intrakine** gene by using retroviral vectors with the truncated low-affinity human nerve growth factor receptor (deltaNGFR) marker, and then isolated by an anti-NGFR antibody/magnetic bead method. The surface expression of CCR-5 in the transduced lymphocytes was dramatically inhibited, as demonstrated by flow cytometric assays. The transduced PBLs were shown to resist various types of M-tropic HIV-1 virus infection. The cell viability, cell proliferation rates, and cell surface markers of the **intrakine**-transduced PBLs were shown to be comparable to those of control PBLs. The transduced PBLs were also found to respond to the stimulation of various CXC- and CC-chemokines, other than RANTES. The transduced PBLs responded to tetanus antigen stimulation by increasing IL-2 production and cell proliferation. In addition, a functionally defective mutant of RANTES that retains its binding activity

to CCR-5, but loses its signaling ability, was used to generate a mutant RANTES **intrakine**. The primary lymphocytes transduced with the mutant RANTES **intrakine** were found to be resistant to M-tropic HIV-1 infection. From these results, we conclude that the primary human lymphocytes transduced with either the wild-type or functionally defective

RANTES **intrakine** are resistant to M-tropic HIV-1 infection, and maintain their basic biological functions. This study, therefore, indicates the potential clinical application of the **intrakine** approach for HIV-1 gene therapy.

L9 ANSWER 10 OF 24 MEDLINE DUPLICATE 2
AN 1999031213 MEDLINE
DN 99031213
TI Genetic co-inactivation of macrophage- and T-tropic HIV-1 chemokine coreceptors CCR-5 and CXCR-4 by **intrakines**.
AU Bai X; Chen J D; Yang A G; Torti F; Chen S Y
CS Department of Cancer Biology, Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.
NC R01-AL41959-01
SO GENE THERAPY, (1998 Jul) 5 (7) 984-94.
Journal code: CCE. ISSN: 0969-7128.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB CC-chemokine receptor (CCR)-5 is the principal coreceptor for the entry of macrophage (M)-tropic HIV-1 viruses into a cell, while CXC-chemokine receptor (CXCR)-4 is the principal coreceptor for T cell line (T)-tropic HIV-1. In this study, we utilized a novel intracellular chemokine (**intrakine**) strategy to co-inactivate genetically both CCR-5 and CXCR-4 in human lymphocytes. The principle of co-inactivation of CCR-5 and CXCR-4 was illustrated by targeting the CC-**intrakine** and CXC-**intrakine** to the lumen of the endoplasmic reticulum (ER) for intracellular blockade of the transport of newly synthesized chemokine coreceptors to the cell surface. The lymphocytes with the phenotypic knock-out of CCR-5 and CXCR-4 were found broadly to resist the infection of M-tropic, T-tropic and dual-tropic HIV-1 viruses. Moreover, the transduced lymphocytes retained normal cell features, including the responsiveness to mitogen and recall antigen stimulation. Thus, this study to our knowledge, is the first to demonstrate that genetic co-inactivation of the M- and T-tropic HIV-1 principal coreceptors in lymphocytes or other cells could be a viable strategy for the long-term control of HIV-1 infection.

L9 ANSWER 11 OF 24 MEDLINE DUPLICATE 3
AN 1998126121 MEDLINE
DN 98126121
TI **Intrakines** and blocking HIV infection: abstract and commentary.
AU D'Souza P
CS Pathogenesis and Basic Research Branch, Division of AIDS, NIAID, National Institutes of Health, Bethesda, Md, USA.. pd6n@nih.gov
SO JAMA, (1998 Feb 11) 279 (6) 476.
Journal code: KFR. ISSN: 0098-7484.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199804
EW 19980403

L9 ANSWER 12 OF 24 MEDLINE
AN 97471007 MEDLINE
DN 97471007

DUPLICATE 4

TI Phenotypic knockout of HIV type 1 chemokine coreceptor CCR-5 by **intrakines** as potential therapeutic approach for HIV-1 infection.
AU Yang A G; Bai X; Huang X F; Yao C; Chen S
CS Department of Cancer Biology, Comprehensive Cancer Center, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157,
USA.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Oct 14) 94 (21) 11567-72.
Journal code: PV3. ISSN: 0027-8424.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199801
EW 19980104

AB A genetic defect in a CC-chemokine receptor (CCR)-5, the principal coreceptor for the macrophage-tropic HIV type 1 (HIV-1), recently was found to naturally protect CCR-5-defective, but healthy, individuals from HIV-1 infection. In this study, we mimic the natural resistance of the CCR-5-defective individuals by designing a strategy to phenotypically knock out CCR-5. The inactivation of the CCR-5 coreceptor is accomplished by targeting a modified CC-chemokine to the endoplasmic reticulum to

block the surface expression of newly synthesized CCR-5. The lymphocytes transduced to express the intracellular chemokine, termed "**intrakine**," were found to be viable and resistant to macrophage-tropic HIV-1 infection. Thus, this gene-based **intrakine** strategy targeted at the conserved cellular receptor for the prevention

of HIV-1 entry should have significant advantages over currently described approaches for HIV-1 therapy.

L9 ANSWER 13 OF 24 MEDLINE
AN 97475198 MEDLINE
DN 97475198

DUPLICATE 5

TI Inactivation of HIV-1 chemokine co-receptor CXCR-4 by a novel **intrakine** strategy [see comments].
CM Comment in: Nat Med 1997 Oct;3(10):1074-5
AU Chen J D; Bai X; Yang A G; Cong Y; Chen S Y
CS Department of Cancer Biology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157, USA.
SO NATURE MEDICINE, (1997 Oct) 3 (10) 1110-6.
Journal code: CG5. ISSN: 1078-8956.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104

AB CXC-chemokine receptor (CXCR)-4/fusin, a newly discovered co-receptor for T-cell line (T)-tropic HIV-1 virus, plays a critical role in T-tropic virus fusion and entry into permissive cells. The occurrence of T-tropic HIV viruses is associated with CD4-positive cell decline and progression to AIDS, suggesting that the T-tropic HIV-1 contributes to AIDS pathogenesis. In this study, we used a novel strategy to inactivate CXCR-4 by targeting a modified CXC-chemokine to the endoplasmic reticulum (ER) to block the surface expression of newly synthesized CXCR-4. The genetically

modified lymphocytes expressing this intracellular chemokine, termed "intrakine", are immune to T-tropic virus infection and appear to retain normal biological features. Thus, this genetic intrakine strategy is uniquely targeted at the conserved cellular receptor for the prevention of HIV-1 entry and may be developed into an effective treatment for HIV-1 infection and AIDS.

L9 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2000 ACS
AN 1997:658824 CAPLUS
DN 127:330222
TI A chemokine trap for HIV co-receptors
AU Lusso, Paolo
CS Dep. Biologial and Technological Res., San Raffaele Scientific Inst., Milan, 20132, Italy
SO Nat. Med. (N. Y.) (1997), 3(10), 1074-1075
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature America
DT Journal
LA English
AB A discussion of the novel anti-HIV strategy of Chen, J.-D., et al., (1997)

which uses modified chemokines (intrakines), trapped within the endoplasmic reticulum, to block expression of HIV co-receptors on the host

cell surface. The purpose of jamming the cell's ER with a crowd of modified chemokines is that the entrapped stromal cell-derived factor-1 (SDF-1) will form intracellular complexes with newly synthesized CXCR4 proteins in the ER, preventing them from reaching the cell surface.

Here,

P. Lusso indicates some of the problems in adapting the system to in vivo results, including specificity and efficiency of transduction, expression of the therapeutic genes, retroviral vectors, and the immunol. competence of the transduced lymphocytes, following their reinfusion into the patient. However, a combination of therapeutic tools (drugs or genes) interfering with the viral life-cycle at several levels, may succeed in maintaining the level of viral replication below the threshold of immunol. damage.

L21 ANSWER 23 OF 77 MEDLINE
AN 96161997 MEDLINE
DN 96161997

DUPPLICATE 15

TI Extension of recombinant human **RANTES** by the retention
of the initiating methionine produces a potent antagonist.
AU Proudfoot A E; Power C A; Hoogewerf A J; Montjovent M O; Borlat F; Offord
R E; Wells T N
CS Glaxo Institute for Molecular Biology, Geneva, Switzerland..
AEP6830@gh.uk.co
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Feb 2) 271 (5) 2599-603.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199605
AB Extension of recombinant human **RANTES** by a single residue at the
amino terminus is sufficient to produce a potent and selective
antagonist.

RANTES is a proinflammatory cytokine that promotes cell
accumulation and activation in chronic inflammatory diseases. When mature
RANTES was expressed heterologously in *Escherichia coli*, the
amino-terminal initiating methionine was not removed by the endogenous
amino peptidases. This methionylated protein was fully folded but
completely inactive in **RANTES** bioassays of calcium mobilization
and chemotaxis of the promonocytic cell line THP-1. However, when assayed
as an antagonist of both **RANTES** and macrophage inflammatory
polypeptide-1 alpha (MIP-1 alpha) in these assays, the
methionylated **RANTES** (Met-**RANTES**) inhibited the
actions of both **chemokines**. T cell chemotaxis was similarly
inhibited. The antagonistic effect was selective since Met-**RANTES**
had no effect on interleukin-8- or monocyte chemotractant
protein-1-induced responses in these cells. Met-**RANTES** can
compete with both [¹²⁵I]**RANTES** and [¹²⁵I]MIP-1 alpha binding to
THP-1 cells or to stably transfected HEK cells recombinantly expressing
their common receptor, CC-CKR-1. These data show that the integrity of
the
amino terminus of **RANTES** is crucial to receptor binding and
cellular activation.

J
L26 ANSWER 3 OF 15 MEDLINE
AN 1998031948 MEDLINE
DN 98031948

DUPLICATE 1

TI Defects in macrophage recruitment and host defense in mice lacking the CCR2 **chemokine** receptor.

AU Kurihara T; Warr G; Loy J; Bravo R

CS Department of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.

SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Nov 17) 186 (10) 1757-62.
Journal code: I2V. ISSN: 0022-1007.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199802

EW 19980204

AB **Chemokines** are a structurally related family of cytokines that are important for leukocyte trafficking. The C-C **chemokine** monocyte chemoattractant protein-1 (MCP-1) is a potent monocyte activator in vitro and has been associated with monocytic infiltration in several inflammatory diseases. One C-C **chemokine** receptor, CCR2, has been identified that mediates in vitro responses to MCP-1 and its close structural homologues. CCR2 has also recently been demonstrated to be a **fusion** cofactor for several HIV isolates. To investigate the normal physiological function of CCR2, we generated mice with a targeted disruption of the **ccr2 gene**. Mice deficient for CCR2 developed normally and had no hematopoietic abnormalities. However, **ccr2(-/-)** mice failed to recruit macrophages in an experimental peritoneal inflammation model. In addition, these mice were unable to clear infection by the **intracellular** bacteria, *Listeria monocytogenes*. These results suggest that CCR2 has a nonredundant role as a major mediator of macrophage recruitment and host defense against bacterial pathogens and that MCP-1 and other CCR2 ligands are effectors of those functions.

L33 ANSWER 13 OF 128 MEDLINE DUPLICATE 7
AN 1998063063 MEDLINE
DN 98063063
TI Impaired monocyte migration and reduced type 1 (Th1) cytokine responses
in C-C **chemokine** receptor 2 knockout mice.
AU Boring L; Gosling J; Chensue S W; Kunkel S L; Farese R V Jr; Broxmeyer H
E; Charo I F
CS Gladstone Institute of Cardiovascular Disease, University of California,
San Francisco 94141-9100, USA.
NC HL-52773 (NHLBI)
DK-53674 (NIDDK)
HL-56416 (NHLBI)
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Nov 15) 100 (10) 2552-61.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199803
EW 19980303
AB Monocyte chemoattractant protein-1 (MCP-1) is a potent agonist for
mononuclear leukocytes and has been implicated in the pathogenesis of
atherosclerosis and granulomatous lung disease. To determine the role of
MCP-1 and related family members in vivo, we used homologous
recombination
in embryonic stem cells to generate mice with a targeted
disruption of C-C **chemokine** receptor 2 (CCR2), the
receptor for MCP-1. CCR2-/- mice were born at the expected Mendelian
ratios and developed normally. In response to thioglycollate, the
recruitment of peritoneal macrophages decreased selectively. In in vitro
chemotaxis assays, CCR2-/- leukocytes failed to migrate in response to
MCP-1. Granulomatous lung disease was induced in presensitized mice by
embolization with beads coupled to purified protein derivative (PPD) of
Mycobacterium bovis. As compared with wild-type littermates, CCR2-/- mice
had a decrease in granuloma size accompanied by a dramatic decrease in
the
level of interferon gamma in the draining lymph nodes. Production of
interferon gamma was also decreased in PPD-sensitized splenocytes from
CCR2-/- mice and in naive splenocytes activated by concanavalin A. We
conclude that CCR2-/- mice have significant defects in both delayed-type
hypersensitivity responses and production of Th1-type cytokines. These
data suggest an important and unexpected role for CCR2 activation in
modulating the immune response, as well as in recruiting
monocytes/macrophages to sites of inflammation.

L33 ANSWER 15 OF 128 MEDLINE DUPLICATE 8
AN 97474771 MEDLINE
DN 97474771
TI Targeted disruption of the beta-chemokine receptor
CCR1 protects against pancreatitis-associated lung injury.
AU Gerard C; Frossard J L; Bhatia M; Saluja A; Gerard N P; Lu B; Steer M
CS Ina Sue Perlmutter Laboratory, Children's Hospital, Department of
Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School
and the Center for Blood Research, Boston, Massachusetts 02115, USA.
NC AI-39759 (NIAID)
HL-52503 (NHLBI)

DK-31396 (NIDDK)
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Oct 15) 0 (8) 2022-7.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB beta-Chemokines and their receptors mediate the trafficking and activation of a variety of leukocytes including the lymphocyte and macrophage. An array of no less than eight beta-chemokine receptors has been identified, four of which are capable of recognizing the chemokines MIP1alpha and RANTES. Genetic deletion of one of the MIP1alpha and RANTES receptors, CCR5, is associated with protection from infection with HIV-1 in humans, while deletion of the ligand MIP1alpha protects against Coxsackie virus-associated myocarditis. In this report we show that the deletion of another receptor for MIP1alpha and RANTES, the CCR1 receptor, is associated with protection from pulmonary inflammation secondary to acute pancreatitis in the mouse. The protection from lung injury is associated with decreased levels of TNF-alpha in a temporal sequence indicating that the activation of the CCR1 receptor is an early event in the systemic inflammatory response syndrome.
L33 ANSWER 16 OF 128 MEDLINE DUPLICATE 9
AN 97311094 MEDLINE
DN 97311094
TI Impaired host defense, hematopoiesis, granulomatous inflammation and type 1-type 2 cytokine balance in mice lacking CC chemokine receptor 1.
AU Gao J L; Wynn T A; Chang Y; Lee E J; Broxmeyer H E; Cooper S; Tiffany H L; Westphal H; Kwon-Chung J; Murphy P M
CS Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
NC R01 HL56416 (NHLBI)
R01 HL54037 (NHLBI)
P01 HL53586 (NHLBI)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Jun 2) 185 (11) 1959-68.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199709
EW 19970901
AB CC chemokine receptor 1 (CCR1) is expressed in neutrophils, monocytes, lymphocytes, and eosinophils, and binds the leukocyte chemoattractant and hematopoiesis regulator macrophage inflammatory protein (MIP)-1alpha, as well as several related CC chemokines. Four other CCR subtypes are known; their leukocyte and chemokine specificities overlap with, but are not identical to, CCR1, suggesting that CCR1 has both redundant and specific biologic roles. To test this, we have developed CCR1-deficient mice (-/-) by targeted gene disruption. Although the distribution of mature leukocytes was normal, steady state and induced trafficking and proliferation of myeloid progenitor cells were disordered in -/- mice. Moreover, mature neutrophils from -/- mice failed to chemotax in vitro and failed to mobilize into peripheral blood in vivo in response to MIP-1alpha. Consistent with this, -/- mice had accelerated mortality when challenged with Aspergillus fumigatus, a fungus controlled principally by neutrophils. To test the role of CCR1 in

granuloma formation, we injected *Schistosoma mansoni* eggs intravenously, and observed a reduction in the size of lung granulomas in $-\text{-}$ mice compared to $+/+$ littermates. This was associated with increased interferon-gamma and decreased interleukin-4 production in $-\text{-}$ versus $+/+$ lung lymph node cells stimulated with egg-specific antigen, suggesting that **CCR1** influences the inflammatory response not only through direct effects on leukocyte chemotaxis, but also through effects on the type 1-type 2 cytokine balance. Thus **CCR1** has nonredundant functions in hematopoiesis, host defense, and inflammation.

L33 ANSWER 17 OF 128 MEDLINE DUPLICATE 10
AN 1998031948 MEDLINE
DN 98031948
TI Defects in macrophage recruitment and host defense in mice lacking the CCR2 **chemokine** receptor.
AU Kurihara T; Warr G; Loy J; Bravo R
CS Department of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Nov 17) 186 (10) 1757-62.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204
AB **Chemokines** are a structurally related family of cytokines that are important for leukocyte trafficking. The C-C **chemokine** monocyte chemoattractant protein-1 (MCP-1) is a potent monocyte activator in vitro and has been associated with monocytic infiltration in several inflammatory diseases. One C-C **chemokine** receptor, CCR2, has been identified that mediates in vitro responses to MCP-1 and its close structural homologues. CCR2 has also recently been demonstrated to be a fusion cofactor for several HIV isolates. To investigate the normal physiological function of CCR2, we generated mice with a targeted disruption of the *ccr2* gene. Mice deficient for CCR2 developed normally and had no hematopoietic abnormalities. However, *ccr2*($-\text{-}$) mice failed to recruit macrophages in an experimental peritoneal inflammation model. In addition, these mice were unable to clear infection by the intracellular bacteria, *Listeria monocytogenes*. These results suggest that CCR2 has a nonredundant role as a major mediator of macrophage recruitment and host defense against bacterial pathogens and that MCP-1 and other CCR2 ligands are effectors of those functions.

L33 ANSWER 20 OF 128 MEDLINE DUPLICATE 13
AN 1998053818 MEDLINE
DN 98053818
TI New strategies for **chemokine** inhibition and modulation: you take the high road and I'll take the low road.
AU McFadden G; Kelvin D
CS Department of Microbiology and Immunology, University of Western Ontario, London, Canada.. mcfadden@rri.on.ca
SO BIOCHEMICAL PHARMACOLOGY, (1997 Dec 15) 54 (12) 1271-80. Ref: 94
Journal code: 9Z4. ISSN: 0006-2952.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204

AB **Chemokines** are low molecular weight cytokines that induce extravasation, motaxis, and activation of a wide variety of leukocytes.

Members of the different **chemokine** families are defined by the orientation of specific critical cysteine residues, and are designated as C-X-C (e.g. interleukin-8), C-C (e.g. regulated upon activation normally

T cell expressed and secreted, RANTES), or C (lymphotoactin). All **chemokines** bind to members of a G-protein coupled serpentine receptor superfamily that span the leukocyte cell surface membrane seven times and mediate the biological activities of the individual ligands. Most **chemokines** possess two major binding surfaces: a high affinity site responsible for specific ligand/receptor interactions and a lower affinity site, also called the heparin-binding or glycosaminoglycan-binding domain, believed to be responsible for the establishment and presentation of **chemokine** gradients on the surface of endothelial cells and within the extracellular matrix.

Although

chemokines are clearly beneficial in wound healing, hemopoiesis, and the clearance of infectious organisms, the continued expression of **chemokines** is associated with chronic inflammation. Therefore, this class of cytokines are attractive targets for the creation of antagonists that abrogate one or more **chemokine** functions. It is envisioned that such antagonists could serve as a new class of anti-inflammatory drugs. In this commentary, we will discuss two

different

but related strategies for antagonizing **chemokine**-induced functions, namely, disruption of the low and high affinity binding sites.

J L33 ANSWER 24 OF 128 MEDLINE

DUPLICATE 16

AN 97223828 MEDLINE

DN 97223828

TI IL-8 **single-chain** homodimers and heterodimers: interactions with **chemokine** receptors CXCR1, CXCR2, and DARC.

AU Leong S R; Lowman H B; Liu J; Shire S; Deforge L E; Gillece-Castro B L; McDowell R; Hebert C A

CS Department of Immunology, Genentech, Inc., South San Francisco, California 94080, USA.

SO PROTEIN SCIENCE, (1997 Mar) 6 (3) 609-17.
Journal code: BNW. ISSN: 0961-8368.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199707

EW 19970705

AB Covalent **single-chain** dimers of the **chemokine** interleukin-8 (IL-8) have been designed to mimic the dimeric form of IL-8 in solution and facilitate the production of heterodimer variants of

IL-8.

Physical studies indicated that use of a simple peptide linker to join two

subunits, while allowing receptor binding and activation, led to self-association of the tethered dimers. However, addition of a single disulfide crosslink between the tethered subunits prevented this multimer from forming, yielding a species of dimer molecular weight. Crosslinked **single-chain** dimers bind to both IL-8 neutrophil receptors CXCR1 and CXCR2 as well as to DARC, as does a double disulfide-linked dimer with no peptide linker. In addition, neutrophil response to these dimers as measured by chemotaxis or beta-glucuronidase release is similar to that elicited by wild-type IL-8, providing evidence that the dissociation of the dimeric species is not required for these biologically relevant activities. Finally, through construction of

single-chain heterodimer mutants, we show that only the first subunit's R motif is the single-chain variants.

L33 ANSWER 30 OF 128 MEDLINE
AN 97386611 MEDLINE
DN 97386611
TI The amino-terminal domain of the CCR2 **chemokine** receptor acts as coreceptor for HIV-1 infection.
AU Frade J M R; Llorente M; Mellado M; Alcami J; Gutierrez-Ramos J C; Zaballos A; Real G; Martinez-A C
CS Department of Immunology and Oncology, Centro Nacional de Biotecnologia, Consejo Superior de Investigaciones Cientificas, Universidad Autonoma de Madrid, Campus de Cantoblanco, E-28049 Madrid, Spain.
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Aug 1) 100 (3) 497-502.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199711
EW 19971101
AB The **chemokines** are a homologous serum protein family characterized by their ability to induce activation of integrin adhesion molecules and leukocyte migration. **Chemokines** interact with their receptors, which are composed of a **single-chain**, seven-helix, membrane-spanning protein coupled to G proteins. Two CC **chemokine** receptors, CCR3 and CCR5, as well as the CXCR4 **chemokine** receptor, have been shown necessary for infection by several HIV-1 virus isolates. We studied the effect of the **chemokine** monocyte chemoattractant protein 1 (MCP-1) and of a panel of MCP-1 receptor (CCR2)-specific monoclonal antibodies (mAb) on the suppression of HIV-1 replication in peripheral blood mononuclear cells. We have compelling evidence that MCP-1 has potent HIV-1 suppressive activity when HIV-1-infected peripheral blood lymphocytes are used as target cells. Furthermore, mAb specific for the MCP-1R CCR2 which recognize the third extracellular CCR2 domain inhibit all MCP-1 activity and also block MCP-1 suppressive activity. Finally, a set of mAb specific for the CCR2 amino-terminal domain, one of which mimics MCP-1 activity, has a potent suppressive effect on HIV-1 replication in M- and T-tropic HIV-1 viral isolates. We conjecture a role for CCR2 as a coreceptor for HIV-1 infection and map the HIV-1 binding site to the amino-terminal part of this receptor. This concurs with results showing that the **CCR5** amino terminus is relevant in HIV-1 infection, although chimeric fusion of various extracellular domains shows that other domains are also implicated. We discuss the importance of CCR2 structure relative to its coreceptor role and the role of anti-CCR2 receptor antibodies in the prevention of HIV-1 infection.
L33 ANSWER 43 OF 128 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 97308933 EMBASE
DN 1997308933
TI [13] Gene targeting strategies to study **chemokine** function in vivo.
AU Cook D.N.
CS D.N. Cook, Department of Immunology, Schering-Plough Research Inst., Kenilworth, NJ 07033, United States
SO Methods in Enzymology, (1997) 287/- (186-206).
ISSN: 0076-6879 CODEN: MENZAU
CY United States
DT Journal; Article

FS 029 Clinical Biochemistry
LA English

L33 ANSWER 79 OF 128 CAPLUS COPYRIGHT 2000 ACS
AN 1998:521376 CAPLUS
DN 129:301259
TI Genetic approaches to the study of **chemokine** function in vivo
AU Cook, Donald N.; Lira, Sergio A.
CS Department of Pathology, University of North Carolina, Chapel Hill, NC,
USA
SO Leukocyte Recruitment Inflammatory Dis. (1996), 259-271. Editor(s):
Peltz, Gary. Publisher: Landes, Austin, Tex.
CODEN: 66ODAR
DT Conference; General Review
LA English
AB A review with 60 refs. Topics discussed include an overview of transgene
and gene **knockout** technol.; mice expressing **chemokine**
transgenes; and anal. of interleukin-8 receptor homolog and **MIP**
-1.**alpha.** **knockout** mice.

L33 ANSWER 88 OF 128 CAPLUS COPYRIGHT 2000 ACS
AN 1995:896295 CAPLUS
DN 123:309606
TI **Antisense** oligonucleotide to **chemokine** for therapeutic
treatment of vascular restenosis
IN Lyle, Leon R.; Thomas-Miller, Beth
PA Mallinckrodt Medical, Inc., USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9519167	A1	19950720	WO 1995-US605	19950113
	W: CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2181035	AA	19950720	CA 1995-2181035	19950113
	JP 09508358	T2	19970826	JP 1995-519178	19950113
	EP 802792	A1	19971029	EP 1995-908532	19950113

R: DE, FR
PRAI US 1994-182917 19940114
WO 1995-US605 19950113
OS MARPAT 123:309606
AB A compn. suitable for administration to a warm-blooded animal is
disclosed
which comprises an **antisense** oligonucleotide to the C-C
chemokine family, typified by MCP-1 and **MIP-1.**alpha.****,
which may or may not be labeled with a radionuclide by means of a chelate
ligand capable of administration to an animal to produce reliable visual
imaging of areas of potential restenosis or to produce therapeutic
effects
on areas of potential restenosis.

L33 ANSWER 92 OF 128 MEDLINE
AN 95397153 MEDLINE
DN 95397153
TI Requirement of **MIP-1** alpha for an inflammatory response to viral
infection.
AU Cook D N; Beck M A; Coffman T M; Kirby S L; Sheridan J F; Pragnell I B;
Smithies O
CS Department of Pathology, University of North Carolina, Chapel Hill
27599-7525, USA.
NC GM20069 (NIGMS)
HL37001 (NHLBI)
DUPLICATE 55

R29HL46195 (NHLBI)

SO SCIENCE, (1995) 15) 269 (5230) 1583-5.
Journal code: US. ISSN: 0036-8075.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199512

AB Macrophage inflammatory protein-1 alpha (**MIP-1 alpha**) is a **chemokine** that has pro-inflammatory and stem cell inhibitory activities *in vitro*. Its biologic role *in vivo* was examined in mice in which the gene encoding **MIP-1 alpha** had been **disrupted**. Homozygous **MIP-1 alpha** mutant (-/-) mice were resistant to Coxsackievirus-induced myocarditis seen in infected wild-type (+/+) mice. Influenza virus-infected -/- mice had reduced pneumonitis and delayed clearance of the virus compared with infected +/+ mice. The -/- mice had no overt hematopoietic abnormalities. These results demonstrate that **MIP-1 alpha** is an important mediator of virus-induced inflammation *in vivo*.

L33 ANSWER 102 OF 128 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:381289 BIOSIS
DN PREV199598395589

TI Role of **MIP-1-alpha** in pulmonary inflammation during an influenza viral infection: Analysis in a **MIP-1-alpha knockout** mouse model.

AU Cook, D.; Beck, M. A.; Jung, J.; Smithies, O.; Sheridan, J. F.

CS Univ. North Carolina, Chapel Hill, NC USA

SO 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 114. The 9th International Congress of Immunology.
Publisher: 9th International Congress of Immunology San Francisco, California, USA.
Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995

DT Conference
LA English

L33 ANSWER 107 OF 128 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:518777 BIOSIS
DN PREV199497531777

TI **Disruption** of the **Scya5/RANTES** gene by homologous recombination.

AU Danoff, Theodore M.; Chiang, Mark Y.; Neilson, Eric G.

CS Penn Center Mol. Studies Kidney Diseases, Renal Electrolyte Hypertension Div., University Pennsylvania, Philadelphia, PA USA

SO Journal of the American Society of Nephrology, (1994) Vol. 5, No. 3, pp. 744.
Meeting Info.: Abstracts Submitted for the 27th Annual Meeting of the American Society of Nephrology Orlando, Florida, USA October 26-29, 1994 ISSN: 1046-6673.

DT Conference
LA English

L33 ANSWER 110 OF 128 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:151108 BIOSIS
DN PREV199497164108

TI **Disruption** of the **SCI/MIP 1-alpha** gene by homologous recombination.

AU Cook, Don N. (1); Coffman, Tom; Kirby, Suzanne L. (1); Plumb, Mark; Pragnell, Ian B.; Smithies, Oliver (1)

CS (1) Dep. Pathol., Univ. North Carolina at Chapel Hill, Chapel Hill, NC USA

SO Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18 PART A,

pp. 24.
Meeting Info.: **Stone Symposium on Hematopoiesis** Breckenridge,
Colorado,
USA January 4-11, 1994
ISSN: 0733-1959.
DT Conference
LA English

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(FILE 'HOME' ENTERED AT 11:25:08 ON 24 MAY 2000)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:25:12 ON 24 MAY 2000
L1 266978 S HIV
L2 241931 S HUMAN IMMUNODEFICIENCY VIRUS
L3 324183 S L1 OR L2
L4 5177 S CORECEPTOR? OR (CO RECEPTOR?)
L5 2715 S L3 AND L4
L6 692 S L5 NOT PY>1997
L7 24489 S CHEMOKINE?
L8 37 S INTRAKINE?
L9 24 DUP REM L8 (13 DUPLICATES REMOVED)
L10 4058 S CCR5 OR CCR3 OR CCR1 OR CXR4
L11 616 S CCR (W) (1 OR 3 OR 5)
L12 1 S CXR(W) 4
L13 14862 S RANTES OR MIP OR MIP1? OR SDF
L14 32902 S L7 OR L10 OR L11 OR L12 OR L13
L15 16634 S L14 NOT PY>1997
L16 316901 S (SIGNAL SEQUENCE?) OR (SIGNAL PEPTIDE?) OR RETENTION
L17 188 S L15 AND L16
L18 230689 S (ENDOPLASMIC RETICULUM) OR GOLGI OR LYSOSOME?
L19 869791 S VESICLE? OR ORGANELLE? OR INTRACELLULAR
L20 1032 S L15 AND (L18 OR L19)
L21 77 DUP REM L17 (111 DUPLICATES REMOVED)
L22 289 S L20 AND (GENE OR CDNA OR VECTOR OR CONSTRUCT)
L23 109 S L20 AND DNA
L24 306 S L22 OR L23
L25 26 S L24 AND (FUSED OR FUSION OR HYBRID OR CHIMERIC)
L26 15 DUP REM L25 (11 DUPLICATES REMOVED)
L27 15710 S SINGLE CHAIN
L28 147 S INTRABOD?
L29 50848 S ANTISENSE
L30 240076 S KNOCKOUT? OR DISRUPT?
L31 304917 S L27 OR L28 OR L29 OR L30
L32 309 S L15 AND L31
L33 128 DUP REM L32 (181 DUPLICATES REMOVED)